REMARKS/ARGUMENTS

The Official Action dated April 9, 2003 has been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested. This reply is submitted with a Request for Continued Examination.

Status of the claims and prosecution:

Claims 1-21 are pending. Claims 3, 5-9 and 16-21 were withdrawn from consideration by the examiner, and claims 1,2, 4 and 10-15 were examined. In the April 9, 2003 Official Action, all examined claims were finally rejected. The claims were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement by the specification, and separately for allegedly lacking an adequate written description in the specification. The rejections under 35 U.S.C. §112, first paragraph, constitute the only remaining grounds of rejection or objection.

Amendments presented in this Reply:

The specification has been amended at paragraph [0115] to correct obvious errors and to effect internal consistency in the specification. Specifically, the content of paragraph [0115] has been amended for consistency with the description of the invention, e.g., as set forth at paragraph [0022] of the substitute specification and elsewhere throughout the specification.

Claim 1 has been amended and claims 2 and 4 have been canceled because their limitations now appears in claim 1. Claim 14 has been amended and new claim 22,

depending from claim 14, has been added. The amendments made herein are made for purposes of clarification and consistency among the claims, as well as to address the election made in response to the restriction requirement. The amendments otherwise do not narrow the claims, nor are they made for any reason substantially related to patentability. No new matter has been added.

Claim 1 has been amended to call for a method for enhancing cytotoxicity elicited by a therapeutic antibody in a subject, which comprises disrupting activation of SHIP by Fc-gamma-receptor IIB (FcγRIIB) caused by binding of the antibody to FcγRIIB, wherein the disrupting is accomplished by modifying the Fc region of the antibody to reduce its affinity for FcγRIIB, thereby inhibiting binding of the antibody to FcγRIIB in the subject. Claim 14 has been amended to call for a method wherein the antibody also binds to activating Fc receptors, and new claim 22 further specifies the method of claim 14, wherein antibody binding is inhibited by modifying the Fc region of the antibody to reduce its affinity for FcγRIIB, while maintaining or increasing its affinity for the activating Fc receptors.

The claims have not been amended to specify the elected species in the independent claim, i.e., methods utilizing antibodies against Her2/neu growth factor receptor or CD20 B cell antigen. Such amendment is premature prior to a determination as to whether the generic claim is allowed.

Applicant asserts that the foregoing claim amendments overcome each of the rejections issued in the April 9, 2003 Official Action, and that the claims as amended are in condition for allowance. Support for Applicant's assertion to this effect is set forth below.

Restatement and clarification of the invention as claimed:

As presently claimed in the sole independent claim, the invention is drawn to a method for enhancing cytotoxicity elicited by a therapeutic antibody in a subject, which comprises disrupting activation of SHIP by FcγRIIB by modifying the Fc region of the antibody to reduce its affinity for FcγRIIB, thereby inhibiting binding of the antibody to FcγRIIB. Contrary to the examiner's assertion at page 3 of the Action, the method of claim 1 does not require retained or enhanced binding of the antibodies to FcγRIIA and FcγRIIIA. That limitation is found in new claim 22.

The specification supports the invention as claimed in claim 1, i.e., without the limitation that antibody binding to FcγRIIA and FcγRIIIA is retained or enhanced. Specifically, at page 6 (paragraph [0016] of the substitute specification), it is stated: "[P]referably, antibody binding is inhibited by modifying the Fc portion of the antibody to reduce its affinity for FcγRIIB." Again at page 14 (paragraph [0048] of the substitute specification), it is stated: "[I]n a preferred embodiment, antibody binding is inhibited by modifying the Fc portion of the antibody to reduce its affinity for FcγRIIB, thus creating an antibody variant." The following paragraph [0049] goes on to state: "[A]n antibody variant with "altered" FcR binding affinity is one which has diminished FcγRIIB binding and enhanced cytotoxicity compared to a parent polypeptide or to a polypeptide comprising a native sequence Fc region." Clearly, nothing in the foregoing statements refers to a requirement for maintaining or enhancing binding affinity for FcγRIIA and FcγRIIIA. This preferred embodiment is discussed in the specification, e.g. at page 7 (paragraph [0022]); however, it is described as a specific embodiment, not as a requirement for the broadest

aspect of the claimed invention (see, e.g., page 16, paragraph [0056], stating: "[I]n a specific embodiment, a modified antibody variant of the invention has reduced affinity for FcRIIB, but unchanged, or even enhanced, affinity for the stimulatory FcRs, FcRI and FcRIII.").

The operability of the method of claim 1 is also supported by the specification. For instance, as described in Example 1, FcγRIIB deficient mice exhibited a profound enhancement of the cytotoxic activity of a therapeutic antibody, as compared with wild-type mice. This enhancement of cytotoxic activity was observed even though no alterations were made in the activating FcRs, FcγRI and FcγRIII.

The invention as claimed is enabled in its full scope by the specification:

The claims stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement on the ground that the specification does not provide sufficient guidance to enable one of skill in the art to use the claimed method for enhancing cytotoxicity elicited by a therapeutic antibody, using a method comprising disrupting SHIP activation by FcγRIIB in a manner reasonably correlated with the scope of the claims. Applicant disagrees, and maintains the traversal as applied to the presently amended claims.

The Examiner bears the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide reasonable expectation as to why scope of protection provided by claim is not adequately enabled by disclosure); MPEP §2164.04. A specification **must** be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective

truth of the statements contained therein which must be relied on for enabling support. *Id.* at 224. As stated in the MPEP:

> [I]t is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d at 224, 169 USPQ at 370.

The present rejection does not satisfy this standard. Citing *In Re Wands*, the examiner has asserted that the specification does not enable the claimed invention due to (1) unpredictability of the art, (2) lack of guidance in the specification, (3) lack of specific working examples, and (4) amount of experimentation required to enable practice of the invention. However, Applicant respectfully submits that the examiner has misjudged the unpredictability of the relevant art, as well as the amount of guidance in the specification and the amount of experimentation required to practice the invention.

The examiner has stated that the art is unpredictable in determining which modifications in the Fc portion of an antibody would be acceptable to retain the functional features needed to practice the invention. The examiner has cited several publications in support of this position. But each of the cited publications relates to modifications in an antigen that affect its antigenicity[1], a subject that is irrelevant to the present invention, which

1 The cited references included (1) Coleman et al. (Res. Immunol. 145: 33-36, 1994) for the proposition that single amino acid changes in an antigen can abolish antigen-antibody binding; (2) Abaza et al. (J. Protein Chem. 11: 433-444, 1992) for the proposition that single amino acid substitutions outside the antigenic site on a protein affect antibody binding; (3) Lederman et al. (Mol. Immunol. 28: 1171-1181, 1991) for the proposition that a single amino acid substitution in a common allele (of an antigen) ablates binding of a monoclonal antibody; and (4) Li et al. (PNAS 77: 3211,3214, 1980) for the proposition that immunoreactivity (i.e., of an antigenic protein) can be dissociated from other biological activities when constructing analogs (not of the antibody, but of the antigen).

relates to the binding of the Fc portion of an antibody to an Fc receptor. Thus, the cited references do not establish that the art surrounding the claimed invention is unpredictable.

In order to practice the claimed invention in its present scope, the skilled artisan would have to treat a subject with a therapeutic antibody having the following characteristics: (1) modified in the Fc region to have reduced affinity for FcγRIIB as compared to an unmodified antibody or natural Fc region; and (2) increased cytotoxicity as compared to an unmodified antibody. Preferably, the antibodies would also have the feature of maintained or enhanced affinity for the activating FcRs. These characteristics can exist in currently available antibodies, in which case the present specification clearly teaches one skilled in the art how to screen for these features. Specifically, Example 1 sets forth two well-accepted animal models for testing cytotoxicity of a therapeutic antibody – the melanoma metastasis model and the tumor xenograft model, each of which was known in the art at the time the present application was filed. An *in vitro* growth inhibition assay is also described in Example 1 as an alternative means of determining cytotoxicity of a therapeutic antibody. For binding affinity of the modified Fc's for Fc receptors, Examples 1 and 2 describe solution-phase and immobilized assays for determining binding affinity of antibodies to various Fc receptors. Such screening assays were well known in the art and utilized routinely.

Furthermore, if a specific antibody with the desired Fc binding properties is not readily available, the present specification provides ample guidance, and it was routine in the art at the filing date, as to how to modify the Fc portion of an antibody and thereafter screen modified antibodies for the desired properties. Specifically, the crystal structure and the amino acid sequence of the human antibody Fc had long been known at the time of filing, thereby enabling rational design of Fc mutants. Example 1 of the instant application

describes how the inventors employed site-directed mutagenesis, using a commercially available kit, to rationally design an Fc mutant. It should be noted, though, that while rational design of mutants was enabled and used to generate Fc mutants, rational design was not a necessity, nor was it the only way to generate mutants at the time of filing. Indeed, it was routine in the art to randomly mutagenize proteins, then screen for mutants with the desired properties, i.e., in the instant case, by using the screening methods and assays described above. Example 2 of the present application describes how the inventors generated a randomly mutagenized Fc library in a yeast expression system, using an error-prone PCR methodology that had been available since 1992.

The law is well settled that a considerable amount of experimentation is permissible (i.e., not "undue") if it is merely routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Angstadt,* 537 F.2d 498, 504 (CCPA, 1976). In the instant application, both conditions are satisfied. First, as discussed above, the specification provides ample guidance as to how to make and screen Fc variants for binding to Fc receptors. Second, the screening of antibodies for specific binding features has been considered routine for many years and, though possibly laborious, has long not been considered to constitute "undue" experimentation. *In re Wands*, 858 F.2d 731, 736 (Fed. Cir. 1988) (methods for . . . screening monoclonal antibodies were well known in 1980), *citing Hybritech Inc. v Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). While the present invention involves screening Fc portions of antibodies for binding to Fc receptors, rather than antigen-binding sites for binding to antigens, the skilled artisan is well guided by the state of the art and the teachings of the

present specification as to how to generate and identify useful antibodies for practice of the invention.

For the foregoing reasons, Applicant asserts that the claims as amended are enabled in their full scope by the specification. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The specification meets the written description requirement for the claimed invention:

The claims also stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description in the specification. Applicant respectfully traverses this rejection.

The Federal Circuit has stated that the test for the written description requirement is "whether the application relied upon 'reasonably conveys to the artisan that the inventor had possession at the time of the . . . claimed subject matter.'" *In re Daniels*, 144 F.3d 1452, 1456, 46 USPQ2d 1788, 1790 (Fed. Cir. 1998). In rejecting a claim under the written description requirement of 35 U.S.C. §112, first paragraph, the examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined in the claims. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976).

The Examiner has failed to meet this burden because of a misinterpretation of the subject matter of the currently pending claims. The examiner asserts that

> [t]he claims as written encompass the genus of antibodies that have a reduce binding affinity for FcRIIB, due to modification of the Fc portion of the antibody, while retaining or enhancing binding to FcRIIA and FcRIIIA that can be used in a method for enhancing cytotoxicity elicited by this antibody *in vivo* . . .

Citing *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d. 1559, 1569 (Fed. Cir. 1997) the examiner next states:

> A description of a genus of antibodies may be achieved by means of a recitation of a representative number of antibodies falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus.

Both of these statements make clear that the examiner's rejection is founded on an erroneous assessment of the claimed subject matter. The standards set forth in *Eli Lilly* pertained to claims in which the claimed subject matter was a genus of DNA molecules. Likewise, in this case, the examiner is applying the standard of *Eli Lilly* as if the claimed subject matter was a genus of antibodies. This is explicitly not the case. Indeed, the originally-filed claims of the instant application did contain claims directed to a genus of antibodies (claims 16-21). However, in the Restriction Requirement issued March 7, 2002, those claims were deemed to cover a patentably distinct invention as compared with the elected claims, and were withdrawn from consideration by the examiner. Accordingly, the adequacy of written description to support the withdrawn antibody claims need not and should not be raised in the application as presently pending.

With respect to the currently pending claims, then, the examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize in Applicant's disclosure a description of the invention as follows:

> A method for enhancing cytotoxicity elicited by a therapeutic antibody in a subject, which comprises disrupting activation of SHIP by Fc-gamma-receptor IIB (FcγRIIB) caused by binding of the antibody to FcγRIIB, wherein the disrupting is accomplished by modifying the Fc region of the antibody to reduce its affinity for FcγRIIB, thereby inhibiting binding of the antibody to FcγRIIB in the subject.

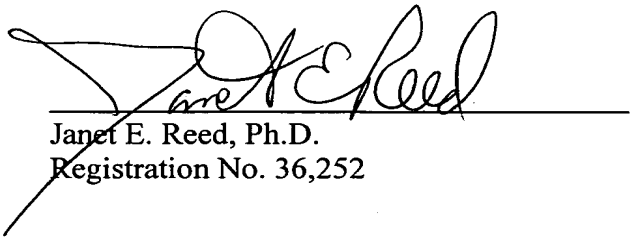
Applicant respectfully avers that the examiner has provided no argument, evidence or reasoning to doubt that the instant specification reasonably conveys to the artisan that the inventor had possession of the above-claimed invention at the time of filing. And indeed, there is no reason to doubt this. As elaborated in the discussion of enablement, the specification provides experimental evidence that cytotoxicity of a therapeutic antibody is enhanced by modifying the Fc portion such that it has reduced affinity for FcγRIIB as compared to an unmodified antibody or natural Fc region. The specification teaches (by example and other description) how to identify or make antibodies with modified Fc regions having the desired features. The specification provides examples of such antibodies. The specification provides at least two assays by which to test for cytotoxicity. In view of the teachings and examples set forth in the specification, one of skill in the art would readily recognize that the inventors were in possession of the invention as claimed, and there has been no argument or evidence put forth by the examiner to conclude otherwise.

For the foregoing reasons, Applicant asserts that the written description requirement of 35 U.S.C.§112, first paragraph, is fully met by the specification to support the currently pending claims. Applicant therefore requests reconsideration and withdrawal of the rejection.

Conclusion:

In view of the claim amendments submitted herewith and the foregoing remarks, the currently pending claims are believed to be in condition for allowance. Applicant respectfully requests early and favorable reconsideration and withdrawal of the objections and rejections set forth in the April 9, 2003 Official Action, and allowance of this application.

Respectfully submitted,



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Janet E. Reed, Ph.D.
Registration No. 36,252

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439